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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,701	10/02/2003	Victor V. Levenson	5369-00011	9778

26753 7590 02/27/2009

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
02/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,701	LEVENSON ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,25-28,31,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,25-28,31,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed November 17, 2008. Currently, claims 1-2, 25-28, 31, 35, 36 are pending.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 17, 2008 has been entered.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

4. Any objections and rejections not reiterated below are hereby withdrawn.

   a. The 103 rejections have been withdrawn in view of each of the claims to require detecting methylation of DAPK as characterizing or diagnosing breast cancer. The prior art does not teach an association between DAPK methylation and breast cancer.

Priority

5. This application claims priority to provisional 60/415,628, filed October 2, 2002.

Drawings

6. The drawings are acceptable.

New Matter

7. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "characterizing ductal breast cancer" are included. The amendment proposes that the new claim language is supported on page 7 of the specification.

Page 7 of the specification states: As used herein, the term "sub-type of cancer" refers to different types of cancer that effect the same organ (ductal cancer, lobular cancer, and inflammatory breast cancer are sub-types of breast cancer.

However, the mere use of ductal on page 7 of the specification does not describe or discuss how to characterize ductal breast cancer as compared with any of the other subtypes of breast cancer. Characterizing breast cancer encompasses detecting a chance of disease-free survival, metastatic disease and progression.

This description does not support characterizing ductal breast cancer. The concept of "characterizing ductal breast cancer" using DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL does not appear to be part of the originally filed invention. Therefore, "characterizing ductal breast cancer" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Newly amended Claims 1-2, 25-28, 31, 35, 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting methylation in DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL in human genes, does not reasonably provide enablement for characterizing any breast cancer based upon methylation profiles for DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL in any subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-2, 25-28, 31 are drawn to a method of diagnosing breast cancer in a subject using plasma sample and detecting the presence of absence of DNA methylation in the promoters of a plurality of genes including DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL.

Claim 35 is directed to a method for characterizing ductal breast cancer in a subject using plasma sample and detecting the presence of absence of DNA methylation in the promoters of a plurality of genes including DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL.

Claim 36 is directed to a method of using plasma sample and detecting the presence of absence of DNA methylation in the promoters of a plurality of genes including DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Maat et al. (Investigative Ophthalmology, Visual Science, Vol 48, No. 2, pages 486-490, February 2007) teaches a positive correlation was found between RASSF1a promoter methylation and development of metastatic disease, however a correlation

with disease-free survival could not be established (abstract). Furthermore, Maat teaches that high frequency of RASSF1A methylation in cell lines compared with primary tumors was observed. Maat also teaches p16 methylation was more common in cell lines than tumors (page 489, col. 2). Thus Maat teaches that promoter methylation in genes is not indicative of any characterization and further that cell lines are not reliable predictors of tumor methylation.

Henrique et al. (Clin Cancer Research, Vol. 13, No. 20, pages 6122-6129, October 2007) teaches methylation patterns of different genes are associated with different characterizing events. For example, APC methylation appears to be associated with clinical Gleason score, however, CCND2, RARB2 are not associated with Gleason score. Henrique further teaches that APC hypermethylation was not significantly found to be associated with disease specific survival (page 6127, col. 1). Moreover, Henrique teaches that from a panel of five genes, CCND2 did not show a significant association with disease-free survival in a univariate analysis (page 6128, col.2).

Suzuki et al. (Cancer Letters, Vol. 242, pages 222-230, 2006) teaches methylation patterns in cancer and finds that aberrant methyylation differed between genes (see Table 4). Moreover, as seen in Figure 2, when analyzed in comparison to stages, different genes were found to have different patterns. Only one gene was significantly associated, namely CRBP1. Further, RIZ1 showed an inverse relationship from all the other genes. Thus it is unpredictable, with out experimentation that is unpredictable whether genes are associated with stages or GS, for example.

Chang et al. (J. Mol. Med, Vol. 83, pages 132-139, 2005) teaches tamoxifen-resistant breast cancers show less frequent methylation of the estrogen receptor B but not the estrogen receptor alpha gene. Chang teaches that the methylation of ERB but

not eh ERA was associated (abstract and Table 2). Thus, each gene is not similarly associated with resistance to drugs.

Maruya et al. (Clinical Cancer Research, Vol. 10, pages 3825-3830, June 2004) teaches cell lines and primary were analyzed and there was variability within and between cell lines and tumor specimens. This supports a heterogeneous and dynamic state of methylation in genes (abstract). Maruya clearly states that cell lines and carcinoma specimens manifest variable levels of methylation (page 3928, col. 2).

House (J. Gastrointest Surg, Vol. 7, pages 1004-1014, 2003) teaches analysis of promoter methylation in numerous genes. House teaches that statistical significance was reached only for tumor necrosis and E-cadherin gene methylation. Further, only E-cadherin methylation and absence of hMLH1 methylation correlated with early tumor recurrence. House analyzed the survival disadvantage at 5 years and found that the promoter status of 10 tumor suppressor genes were not significant as prognostic markers (page 1009, col. 1-2).

The newly amended claims particularly claim plasma samples for detecting breast cancer. However, the post-filing date art makes it clear that DAPK is not specifically methylated in breast cancer. Yang et al (Gynecologic Oncology, Vol. 93, pages 435/-440, 2004) teaches detection of hypermethylated genes in tumor and plasma of cervical cancer patients. Table 2, page 437 illustrates, DAPK is methylated in plasma of cervical cancer patients.

Similarly, Miyamoto et al. (Jpn, J. Clin, Oncol, Vol. 35, No. 6, pages 293-301, 2005) teaches cancer-derived DNA in plasma by DNA methylation. DAPK and a plurality of other gene were analyzed in plasma and detected in Head and neck cancer (see Table 2, pages 296).

Guidance in the Specification.

The specification teaches methylation profiling in lymphoma cell lines (Figure 7). DAPK and PR are illustrated. For DAPK, 0% of the 8 controls have methylation while 33% of the T-cell lines were methylated. Similarly, for PR, 0% of the 8 control samples have methylation while 50% of the T-cell lines were methylated.

Table 1, page 76, illustrates differences between two cell lines. For example DAPK, was methylated in MCF7, but not methylated in T47D wt. Thus, cell lines do not appear to consistently demonstrate methylation.

The specification detects methylation in MDA-MD-231 breast cancer cell lines treated with 5-aza-2' deoxycytidine (page 77). The specification teaches analysis of 10 samples from patients. The specification fails to provide any results of the analysis, in particular with respect to DAPK or PR.

Figure 2 illustrates the methylation of 40 promoters in breast tumor tissue and normal breast tissue. As seen, the methylation of DAPK is unpredictable. DAPK is methylated in 5/5 normal tissues and in 4/5 breast tumor tissues (page 79). Moreover, PR is similarly methylated unpredictable.

Figure 3 illustrates each of the eight claimed genes and methylation patterns in various samples.

Applicants have provided a declaration to support the teachings in the specification. Paragraph 4 of the declaration states that 29 plasma samples from normal patients or 29 samples from patients with DCIS were obtained. The declaration analyzes the methylation of DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL in plasma of DCIS (ductal carcinomas in situ) patients and healthy controls. Table 3 of the declaration illustrates that DAPK1 in DCIS is methylated 89.3% of the time whereas normal is methylated 51.9% of the time.

Table 4 of the declaration is described in paragraph 4 as teaching the biomarker comprising DAPK1 and additional genes was shown to identify DCIS with approximately 84% sensitivity and 90% specificity. The declaration fails to show which additional genes were used and how many additional genes, and whether any combination of genes would be significant.

Table 5 of the declaration is describes as plasma samples from three healthy patients or three plasma samples from patients with ADH (atypical ductal hyperplasia)(see paragraph 5 of the declaration). However the grant proposal appears to indicate that 8 samples of each were used. This appears to be a discrepancy between the explanation and the table. Moreover, ADH appears to be a benign condition and not be breast cancer, as particularly claimed in the pending claims. Finally the grant proposal indicates that "our experience indicates that genes with 20% methylation difference in the trial set almost always become components of the composite biomarker, suggesting that 18 genes can contribute to ADH biomarker." The instant claims are not directed to a composite biomarker of 18 genes. Thus, the declaration does not appear to be commensurate in scope with the claims.
The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

The specification has no working examples of characterizing cancer for detecting chemotherapy resistant cancer, chance of disease free survival, risk of developing metastatic disease, monitoring progression.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

All of the claims are broadly drawn to any subject. The specification and the declaration appear to be limited to humans. The specification does not provide any guidance as to the methylation patterns in dogs, cat, monkeys, for example. It is unpredictable that each of these subjects would be similarly methylated in any predictable manner.

Claims 1-2, 25-28, 31, for example are specifically drawn to diagnosing breast cancer in a plasma sample by DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL methylation patterns. The specification is silent with respect to any working examples of DAPK, FAS, MCTS, p16, PAX5, THBS, TRANCE, VHL methylation patterns in plasma. The declaration filed April 29, 2008 appears to illustrate in DCIS patients, not any breast cancer, a difference between methylation in plasma of DCIS patients and healthy controls (89.3% v. 51.9% for DAPK, for example). It is noted there is no explicit p-value or statistical analysis for this biomarker. The analysis in the declaration for ADH has been considered, but does not appear to be within the scope of the claims, since the claims are drawn to breast cancer and not hyperplasia. Moreover, the sample size for the ADH analysis uses either 3 or 8 patients which is statistically small and lacks informative value. Finally, the claims appear to encompass a method of taking a plasma sample from any subject, analyzing the plasma for methylation and assessing whether the individual has breast cancer. The post-filing date art suggest that at least two other cancers have high levels of methylation of DAPK in plasma. Thus, a method of screening patients for DAPK methylation in plasma would not indicate whether the subject had breast, head and neck or cervical cancer without further experimentation.

Moreover, the absence of DNA methylation would not indicate an absence of breast cancer predictably. Breast cancer is affected by many genetic pathways which would similarly include BRAC1 or BRAC2 mutations. Thus, the subject may have an absence of methylation of DAPK but possess BRAC1 mutations and thus would have breast cancer. The specification and the declaration do not support the absence of methylation is indicative of the absence of breast cancer in the subject. Thus, given the claims are broadly drawn to any breast cancer and the declaration is directed only to ductal cancer and the very small sample size, it is unpredictable whether the skilled artisan would be able to diagnose any breast cancer using the guidance provided in the specification.

Claim 35 is directed to a method for characterizing ductal breast cancer in a subject. Characterizing ductal breast cancer encompasses detecting a chance of disease-free survival, metastatic disease and progression. The specification fails to provide any guidance of how to characterize the ductal breast cancer in such a manner. The art clearly teaches that different genes are differentially associated with disease-free survival, metastatic disease and progression. The art teaches numerous situations where methylation patterns could not be established to be associated with a chance of disease-free survival, metastatic disease and progression. For example, Maat teaches a positive correlation was found between RASSF1a promoter methylation and development of metastatic disease, however a correlation with disease-free survival could not be established (abstract). Moreover, House teaches analysis of promoter methylation in numerous genes. House teaches that statistical significance was reached only for tumor necrosis and E-cadherin gene methylation. Further, only E-cadherin methylation and absence of hMLH1 methylation correlated with early tumor recurrence. House analyzed the survival disadvantage at 5 years and found that the

promoter status of 10 tumor suppressor genes were not significant as prognostic markers (page 1009, col. 1-2). Therefore, for each particular gene and each particular "characterization" of disease-free survival, metastatic disease and progression, individual experimentation which is unpredictable and undue would be required. The experimentation would be trial and error experimentation with no expectation of success.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the lack of association between genes and different characterizations including disease-free survival, metastatic disease and progression, the broad scope of the claims would require significant unpredictable and undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner

that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts the skilled artisan would be able to diagnose or characterized breast cancer in a subject as supported by the Declaration by inventor Dr. Vicro V. Levenson. The response asserts that the DAPK1 gene and additional genes were used together as a composite "biomarker". This argument has been considered but is not convincing because the declaration and specification do not provide the composite biomarkers which allow detection of breast cancer in plasma. The MPEP requires in 2164.05, "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Here, the declaration regarding the composite biomarker of 10 genes is not persuasive because the declaration and the specification do not provide such a composite biomarker and

furthermore, the claims do not appear to be reasonably correlated to the scope of the claimed invention directed to 8 markers. While the declaration demonstrates that the 8 genes required by the claims are over methylated compared with normal patient samples, the sample size is extremely small. Moreover, the claims are not limited to Ductal breast cancer. It is noted that the new matter rejection above, raises concern regarding the new matter of ductal breast cancer.

Second, the response asserts that the methylation status of p16 in plasma is recognized in the art as being diagnostic for breast cancer, citing Silva 199 and Silva Silva 199 is directed to methylation status in exon 1 of 5 plasma patients. Silva teaches that in 5 (14%) of the 8 patients that showed methylation in tumor DNA, the phenomenon was demonstrated in plasma DNA. Thus, in 5/35 patients with breast cancer, this was seen. The instant claims are drawn to promoters. The teachings of Silvai are directed to exon 1. Thus, the teachings of Silva do not appear to be commensurate in scope with promoters as required by the instant claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 36 has been added and merely requires a "method". Step "a" requires providing a plasma sample from "the subject." "The subject" appears to lack proper antecedent basis. The claim does not previously refer to "a subject. Appropriate correction is required.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634
February 27, 2009